REMARKS

Claim disposition

Claims 3 is cancelled.

Claims 1, 4, 5, 6, and 7 are amended as explained below. New claim 10 is added. Claims 1-2, and 4-10 will be pending in the application upon entry of this amendment.

Re paragraph 4 of the Office Action under the heading, Information Disclosure Statement

The Office Action indicates that the reference DE 19802327 A1 submitted as part of the information disclosure statement filed December 17, 2001 has not been considered, because no translation of the document has been provided to the office. Applicants' records indicate that a translation was submitted to the office as part of the December 17, 2001 filing. Applicants hereby provide copies of the face sheets of the reference and the translation, each bearing the express mailing label number EF378134388US used for the December 17, 2001 submission, as evidence that this submission included the translation.

Nevertheless, Applicants resubmit another copy of the translation herewith (7 pages total), and request that the above-stated reference be considered.

Withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested

Claims 5 was rejected under 35 U.S.C. § 112, first paragraph; the Office Action indicating lack of enablement for this claim reciting "a pharmaceutical composition with a ratio from 1:1 to 250:1 by weight". Claim 5 is amended to recite "A pharmaceutical composition according to claim 1 wherein the ratio of gabapentin to pregabalin is from 1:1 to 250:1 by weight". Thus, this rejection is obviated by this amendment of claim 5 which includes the recitation "of gabapentin to pregabalin"; such recitation having been inadvertently excluded from the original claim. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested

Claims 3 was rejected under 35 U.S.C. § 112, second paragraph; the Office Action indicating lack of enablement as the basis. This rejection is obviated by the cancellation of claim 3. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Withdrawal of the rejections under 35 U.S.C. § 102, is respectfully requested

Claims 5 was rejected under 35 U.S.C. § 102 (b), for anticipation by U.S. Patent 5,721,242 (Kompis *et al.*). The Office Action indicates that the claim reads on any composition having a ratio from 1:1 to 250:1 by weight and Kompis et al. disclose an antibiotic composition comprising epiroprim and dapsone wherein the ratio of epiroprim to dapsone is in the ratio of about 1:1 to about 2:1 by weight.

As stated above, claim 5 is amended to recite "A pharmaceutical composition according to claim 1 wherein the ratio of gabapentin to pregabalin is from 1:1 to 250:1 by weight". Thus, claim 5 now excludes the above-explained antibiotic compositions of Kompis *et al.* Therefore, Applicants respectfully request that this rejection of claim 5 under 35 U.S.C. § 102, first paragraph, be withdrawn.

Claims 1-2, 6-7 and 9 were rejected under 35 U.S.C. § 102 (e), for anticipation by U.S. Patent 6,451,857 B1 (Hurtt *et al.*). The Office Action states that "Hurtt teaches a composition comprising two or more anti-epileptic compounds combined with one or more compounds selected from NSAID, analgesic, NMDA receptor antagonists, or combinations thereof, namely gabapentin/pregabalin/opioid, gabapentin/pregabalin/NSAID, gabapentin/pregabalin/naproxen (column 5, lines 38-49), that is useful for treating pain including inflammatory pain (column 5, 50-60 and column 6, lines 8-19) wherein said composition is prepared in unit dosage form (column 6, lines 20-45)". See final paragraph, page 7, of the Office Action. The Office Action further states that "[a]lthough Hurtt is silent about "synergistic effect" in independent claim 1, such preamble to the claim is not limiting to the interpretation of the composition. Thus, the referenced composition anticipates the claimed invention ". See second paragraph, page 8, of the Office Action.

Independent claims 1, 6, and 7 have each been amended to include the recitation "wherein said effective amounts have a synergistic effect in the treatment of pain." Support for this amendment is present throughout the specification and the original claims. For example, see page 3, line 16 of the specification; the original claims and the EXAMPLES. The recitation clearly presents the "synergistic effect" of "said effective amounts" of gabapentin and pregabalin as stated in the claims under consideration, as a limitation of these claims. As explained above, and stated in the Office Action, Hurtt *et al.* is silent about synergistic effect. As Hurtt et al. do not teach this limitation of the claims under consideration, Applicants submit that the claims are not anticipated by Hurtt *et al.* Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 102, be withdrawn and not extended to new claim 10.

Withdrawal of the rejections under 35 U.S.C. § 103, is respectfully requested

Claims 3, 4, and 8 were rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent 6,451,857 B1 (Hurtt *et al.*). The Office Action indicates that the determination of the ratios or dosages of the claimed inventions under consideration are within the skill of the ordinary skilled artisan who "would be motivated to determine optimum amounts to get the maximum effect of the drug".

Applicant submits that it is well established that motivation to try, without more, is not the proper standard to establish a *prima facie* case of obviousness. Rather, while the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references; the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made and not in hindsight; and the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001; *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

As stated above, independent claims 1, 6, and 7 have each been amended to include the recitation "wherein said effective amounts have a synergistic effect in the treatment of pain"; which clearly presents the "synergistic effect" of "said effective amounts" of gabapentin and pregabalin as stated in the claims under consideration, a limitation of these claims. As more fully explained above, and stated on page 7 of the Office Action, final paragraph, Hurtt et al. teach specific combinations consisting of gabapentin, pregabalin, a third compound. Moreover, as more fully explained above, and stated on page 8 of the Office Action, second paragraph, Hurtt et al. is silent about synergistic effects. Therefore, the reference does not teach or suggest the limitation of synergistic effect. Nor does Hurtt *et al.* contain any suggestion or incentive that would have motivated the skilled artisan to modify the combinations referred to in Hurtt *et al.* to arrive at the claimed compositions with the limitation of synergistic effect therein; let alone with a reasonable expectation of success. Therefore, Applicants submit that the claims under consideration are not *prima facie* obvious over Hurtt *et al.* Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 103, be withdrawn and not extended to new claim 10.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is respectfully solicited.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 that may be required by this paper to Deposit Account No: 23-0455.

In the event the Examiner wishes to discuss any matter concerning this application, he is welcomed to communicate with the undersigned by telephone.

Respectfully submitted,

June 22, 2004

Mehdi Ganjeizadeh
Reg. No. 47,585
Warner-Lambert Company LLC
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (734) 622-3831
Fax (734) 622-2928

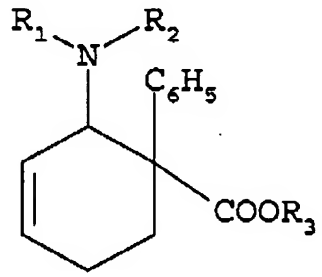
GÖDECKE AKTIENGESELLSCHAFT BERLIN PD6375

Synergistic medicinal composition with analgesic action

Description

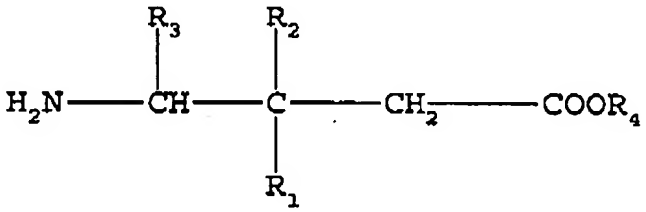
The invention concerns synergistic medicinal compositions with analgesic action containing an active material combination consisting of

a) a basic-substituted cyclohexene of the general formula I



wherein R_1 and R_2, which can be the same or different, signify an alkyl radical with 1 to 6 C-atoms or two alkylene radicals linked with one another and R_3 an alkyl radical with 1 to 6 C-atoms and
□

b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II



wherein R_1 signifies a straight-chained or branched alkyl radical with 1 to 6 C-atoms, phenyl or cycloalkyl with 3 to 6 C-atoms, R_2 hydrogen or methyl or R_1 and R_2, together with the C-atom, signify cycloalkyl with 4 to 6 C-atoms, R_3 is hydrogen, methyl or carboxyl and R_4 is hydrogen or an alkyl group with 1 to 6 C-atoms, as well as pharmacologically compatible and pharmaceutically acceptable salts of the compounds of the general formula I and II.

Compounds of the general formula I are preferred in which R_1 and R_2 are the same or different and signify hydrogen or a methyl group and R_3 an ethyl group. Especially preferred are (±)-ethyl-(trans-2-dimethylamino-1-phenyl-3-cyclohexen-trans-1-carboxylate (tilidine) and (±)-ethyl-(trans-2-(methylamino)-1-phenyl-3-cyclohexene-trans-1-carboxylate (nortilidine) or their enantiomers, as well as their salts, preferably the hydrochloride or the dihydrogen orthophosphate.

Preferred compounds of the general formula II are those in which R_1 is hydrogen, R_2 an isobutyl group or R_1 and R_2, together with the C-atom, a cyclohexyl group and R_3 and R_4 is hydrogen. Especially preferred are aminomethyl-1-cyclohexane-acetic acid (gabapentin), 3-aminomethyl-5-methylhexanecarboxylic acid and ist enantiomer (S)-3-aminomethyl-5-hexanecarboxylic acid (pregabalin).

Compounds of the general formula I are known from DE-A 1 518 959, compounds of the general formula II are described, for example, in WO 93/23383 for the treatment of epileptic attacks.

Because of the basic nature of the compounds of the general formula I, salts of the acidic compounds of the general formula II are also formed directly.

The compounds of the general formulae I and II, as well as their salts or addition salts of both can be used in usual compositions and in mixtures with usual pharmaceutically acceptable carriers or dilution agents.

The compositions according to the invention can be administered orally, topically or parenterally in liquid or solid form. As

injection solution, above all water is used which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents or buffers.

The compositions can be present as usual galenical formulations, such as e.g. tablets, capsules, dragees, plasters, emulsions or salves. They are prepared in that one incorporates the compounds or their salts in per se known manner into a pharmacologically acceptable carrier material and possibly suitable additives.

Such additives are e.g. tartrate or citrate buffers, ethanol, complex formers (such as ethylene-diamine-tetraacetic acid and its non-toxic salts), as well as high molecular polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials are e.g. starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, anirnal and vegetable fats, solid high molecular polymers (such as polyethylene glycol); compositions suitable for oral administration can, if desired, also contain additional flavouring and/or sweetening materials.

Compounds of the general formula I, especially tilidine, possess an average analgesic potency. The action of tilidine can admittedly be increased in limited way by increasing of the dosage but, in the case of greatest pains, must be exchanged for more potent active materials, such as e.g. morphine.

The structural analogues of glutamic or gamma-aminobutyric acid according to general formula II, especially gabapentin and pregabalin, are known for their effectiveness in the case of cerebral convulsive attacks. In the case of the clinical use of gabapentin, it is found that this additionally possesses an analgesic effectiveness, especially in the case of neuropathic pains, whereby, however, the action mechanism is still not clarified.

Surprisingly, it has been found that the combination of both active materials permits a distinctly lower dosing than the individual

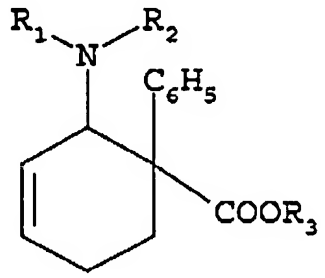
use, whereby an analgesic action is exhibited which exceeds by far the maximum action of the individual components and is thus more than additive. In addition, it has been found that an active material combination according to the invention is intrathecally administratable and, in contradistinction to the cornpounds of the general formula I which, administered in this way, are ineffective, exhibit an unexpectedly high analgesic action which, in comparison with the normal enteral or parenteral administration, makes possible a further considerable reduction of the amount of active material used.

With the active material combination according to the invention, there are made available extremely potent analgesic medicinal combinations with minimal side effects, the analgesic potency of which lies in the range of strong opioids, such as morphine or fentanyl. Due to the synergistic action of the combination, which above all has an effect on the compounds of formula I, the dosaging of these components can be kept very low. This has the additional advantage that the risk of misuse is considerably reduced and a development of tolerance, as well as the possible euphorising effect of strong analgesics, is countered. Therefore, by means of the combination according to the invention, there is made available a medicament superior to all hitherto strong analgesics since compounds of the formula II do not show these undesired properties of conventional strong analgesics.

Claims

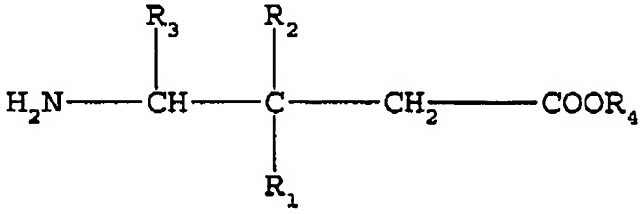
1. Medicinal composition with analgesic action, containing an active material combination consisting of

a) a substituted cyclohexen of the general formula I



wherein R_1 and R_2, which can be the same or different, signify an alkyl radical with 1 to 6 C-atoms or two alkylene radicals linked with one another and R_3 an alkyl radical with 1 to 6 C-atoms and

b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II



wherein R_1 signifies a straight-chained or branched alkyl radical with 1 to 6 C-atoms, phenyl or cycloalkyl with 3 to 6 C-atoms, R_2 hydrogen or methyl or R_1 and R_2, together with the C-atom, signify cycloalkyl with 4 to 6 C-atoms, R_3 is hydrogen, methyl or carboxyl, and R_4 is hydrogen or an alkyl group with 1 to 6 C-atoms, as well as pharmacologically

compatible and pharmaceutically acceptable salts of the compounds of the general formula I and II.

2. Medicament according to claim 1, characterised in that, for compounds of the general formula I, R_1 and R_2 are the same or different and signify hydrogen or a methyl group and R_3 an ethyl group and, for compounds of the general formula II, R1 signifies hydrogen, R_2 an isobutyl group or R_1 and R_2, together with the C-atom, signify a cyclohexyl group and R_3 and R_4 hydrogen.

3. Medicaments according to claim 1 or 2, containing

a) tilidine and/or nortilidine and

b) gabapentin and/or pregabalin.

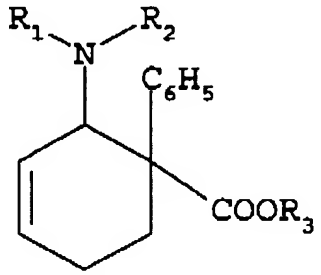
4. Medicaments according to claims 1 to 3 containing the pharmacologically most effective enantiomers of the components.

5. Use of compounds of the general formulae I and II according to claims 1 to 4 for the preparation of medicaments for the treatment of pain.

Summary

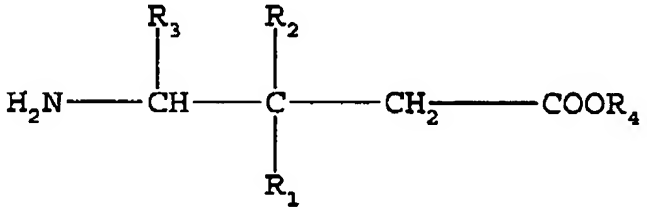
The invention concerns synergistic medicinal compositions with analgesic action containing an active material combination consisting of

a) a substituted cyclohexene of the general formula I



and

b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II



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(71) Anmelder:
Gödecke AG, 10587 Berlin, DE

(72) Erfinder:
Brennscheidt, Ulrich, Dr.med., 79312 Emmendingen, DE

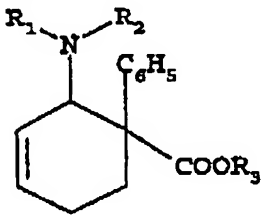
cc: Diane Leonie

Express Mail No. EF378134388US

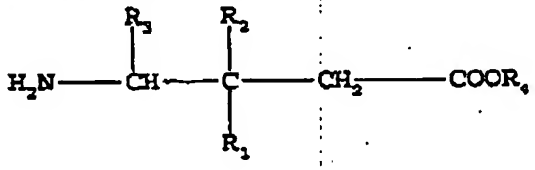
Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) Synergistische Arzneimittelzubereitung mit analgetischer Wirkung

(57) Die Erfindung betrifft synergistische Arzneimittelzubereitungen mit analgetischer Wirkung, enthaltend eine Wirkstoffkombination bestehend aus
a) einem substituierten Cyclohexen der allgemeinen Formel I



und
b) einem Glutaminsäure- bzw. Gammaaminobuttersäureanalogen der allgemeinen Formel II.



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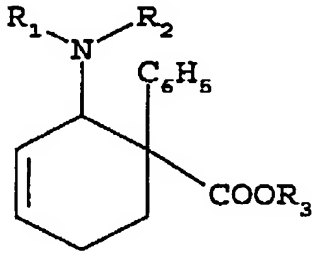
Synergistic medicinal composition with analgesic action

Description

The invention concerns synergistic medicinal compositions with analgesic action containing an active material combination consisting of

a) a basic-substituted cyclohexene of the general formula I



wherein R_1 and R_2, which can be the same or different, signify an alkyl radical with 1 to 6 C-atoms or two alkylene radicals linked with one another and R_3 an alkyl radical with 1 to 6 C-atoms and

b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II